Physical fatigue characterises patient experience of primary Sjögren's syndrome

S. Arends[1], P.M. Meiners[2], R.V. Moerman[1], F.G.M. Kroese[1], E. Brouwer[1], F.K.L. Spijkervet[2], A. Vissink[2], H. Bootsma[1]

[1]Department of Rheumatology and Clinical Immunology, [2]Department of Oral and Maxillofacial Surgery, University of Groningen, University Medical Center Groningen, the Netherlands.

Abstract

Objective

Besides ocular and oral dryness, fatigue is a major symptom in patients with primary Sjögren's syndrome (pSS). Our aim was to investigate the importance of fatigue in relation to other symptoms experienced as well as to evaluate the effect of rituximab treatment on fatigue in pSS patients with active disease.

Methods

This analysis was based on data from our open-label rituximab study in 28 pSS patients. Symptoms of dryness, physical fatigue, pain, and mental fatigue were scored on 0-10 scales (according to ESSPRI). Systemic disease activity was assessed with ESSDAI.

Results

At baseline, 24 (86%) patients rated physical fatigue as the complaint most eligible for improvement (median importance of 10), followed by pain, dryness, and mental fatigue. After rituximab treatment, physical fatigue showed maximum improvement of 2.5 points and 31% in median values at group level, and 10 (36%) patients reached physical fatigue score<5 representing patient-acceptable symptom state (PASS). In comparison, systemic disease activity improved 5.5 points and 73% at group level, and 22 (79%) patients reached ESSDAI<5 representing low disease activity. GEE analysis over time revealed that physical fatigue was significantly associated with absolute number of B cells, dryness and mental fatigue, but not with ESSDAI, IgG levels and IgM-RF.

Conclusion

Physical fatigue characterises patient experience of pSS. Rituximab treatment resulted in significant improvement of patient-reported symptoms. However, the large majority of patients still experienced physical fatigue at an unsatisfactory level, above the cut-off value for PASS. Therefore, attention for optimal management of this prominent symptom is warranted.

Key words

primary Sjögren's syndrome, fatigue, patient-reported outcome, rituximab, patient-acceptable symptom state

Suzanne Arends, PhD
Petra M. Meiners, MD, PhD
Rada V. Moerman, MD
Frans G.M. Kroese, PhD
Elisabeth Brouwer, MD, PhD
Frederik K.L. Spijkervet, MD, PhD
Arjan Vissink, MD, PhD
Hendrika Bootsma, MD, PhD

Please address correspondence to:
Suzanne Arends, PhD,
University Medical Center Groningen,
Rheumatology and Clinical Immunology,
P.O. Box 30001,
9700 RB Groningen, the Netherlands.
E-mail: s.arends@umcg.nl

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Introduction

Primary Sjögren's syndrome (pSS) is one of the most common systemic autoimmune diseases. Besides ocular and oral dryness, fatigue is a major symptom in patients with pSS. The reported prevalence rates of abnormal fatigue range from 30 to 88% in pSS, depending on the study population and measurement instrument applied (1-5). Qualitative interviews with 9 patients demonstrated that pSS-related fatigue clearly differs from ordinary tiredness. Patients reported that their fatigue is not only characterised by a heavy and persistent lack of vitality, but also by unpredictable and uncontrollable daily fluctuations (6). Importantly, fatigue was found to be associated with reduced health-related quality of life, impaired daily functioning, and work disability in pSS (7-11).

Fatigue can be divided into different dimensions, *e.g.* physical, mental, motivational, and affective fatigue (12). A good measurement instrument for fatigue should be reliable, sensitive to change, and easy to administer (12). Validated questionnaires in pSS are one-dimensional, such as a single item questionnaire on global fatigue (13), and multi-dimensional such as the multi-dimensional fatigue index (MFI) and the profile of fatigue (PROF) (2, 14).

The importance of fatigue in pSS is illustrated by the fact that it is frequently included in the composite primary endpoints of randomised controlled trials (RCTs) evaluating the effect of systemic treatment in pSS (15-18). Fatigue is also part of the validated EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) and the recently proposed Sjögren's Syndrome Responder Index (SSRI) (19, 20). From the patient perspective, it is meaningful to achieve a satisfactory state of well-being, also referred to as patient-acceptable symptom state (PASS) (21, 22).

The aim of the present analysis was to investigate the importance of fatigue in relation to other symptoms experienced as well as to evaluate the effect of rituximab treatment on subjective assessment of fatigue in pSS patients with active disease.

Methods

The present analysis regarding patient experience of fatigue was based on data from our open-label rituximab study (23). As described previously, 28 pSS patients were treated with rituximab 1000 mg intravenously at days 1 and 15. In 8 patients, this was their first course of rituximab treatment. In 20 patients, retreatment was started after recurrence of clinical symptoms. All patients fulfilled the revised American-European Consensus Group (AECG) criteria for pSS and were over 18 years of age. The study protocol was approved by the ethics committee of the University Medical Center Groningen (UMCG; METc2008.179) and all patients provided written informed consent.

Clinical assessments

Patients were evaluated at baseline and 16, 24, 36, 48, and 60 weeks after (re) treatment with rituximab. At all visits, subjective symptoms of dryness, physical fatigue, and pain (joint or muscle pain in arms or legs) were scored on a numerical rating scale (NRS; on a scale of 0–10) according to the ESSPRI. ESSPRI total score was calculated as the mean of dryness, physical fatigue, and pain (13). Mental fatigue (unable to think clearly, have difficulty to concentrate, forgetfulness or making mistakes) was also scored on NRS of 0–10. Patient-acceptable symptom state (PASS) refers to the highest level of symptoms beyond which patients consider themselves well. For ESSPRI, a lower score means fewer complaints. According to the analyses of Seror *et al.*, PASS was defined as score <5 [22]. At baseline and during follow-up, patients were asked to rank their symptoms of dryness, physical fatigue, pain, and mental fatigue in order of importance; from 1: most eligible for improvement to 4: least eligible for improvement. In addition, the importance for improvement of each symptom was scored on NRS of 0–10.

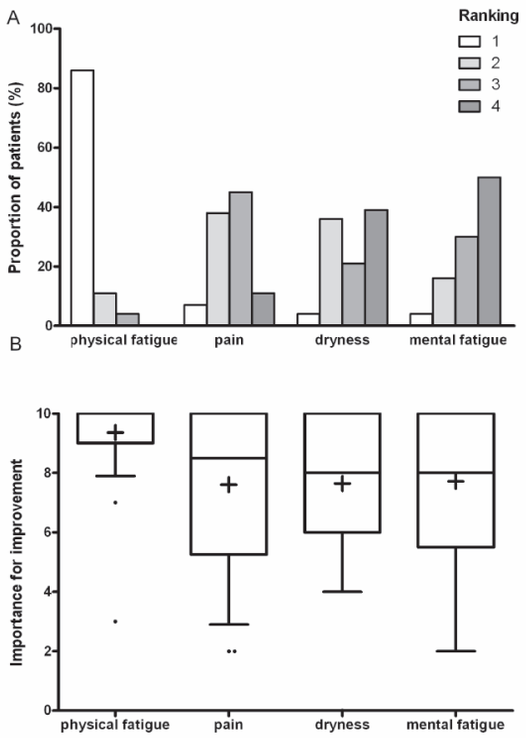
Fatigue was assessed in more detail using the Multidimensional Fatigue Inventory (MFI). The MFI consists of 5 domains (all ranging from 0–20); general fatigue, physical fatigue, reduced activity, reduced motivation, and men-

Table I. Baseline characteristics of the pSS study population (n=28).

Female gender (n, %)	27 (96)
Age (years)	43 ± 14
Time since diagnosis (years)	5.3 (3.8-9.9)
B cells (10^9/L)	0.27 ± 0.15
IgG (g/L)	22.5 ± 7.4
IgM-RF (kIU/L)	90 (30-220)
Anti-Ro/SSA positive (n, %)	28 (100)
Anti-La/SSB positive (n, %)	20 (71)
UWS (mL/min)	0.10 (0.03-0.27)
SWS (mL/min)	0.31 (0.16-0.58)
ESSPRI total score	6.7 (5.0-8.2)
Physical fatigue	8 (6-9)
Pain	7 (4-8)
Dryness	7 (3-8)
Mental fatigue	5.5 (3-7)
MFI total score	67.2 ± 18.9
General fatigue	18 (15-19)
Physical fatigue	16 (12-19)
Reduced activity	12.5 (10-16)
Mental fatigue	11 (8-15)
Reduced motivation	12.5 (9-14)
ESSDAI total score	8.0 ± 4.5

Values are presented as mean ± SD or median (IQR), unless otherwise indicated.
RF: rheumatoid factor; USW: unstimulated whole salivary flow rate; SWS: stimulated whole salivary flow rate; MFI: Multidimensional Fatigue Inventory; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index.

Fig. 1. Order of importance (**A**) and importance for improvement (**B**) of physical fatigue, pain, dryness, and mental fatigue according to the 28 pSS patients with active disease before start of rituximab treatment.



tal fatigue (24). MFI total score was calculated as the sum of the 5 domain scores.

Systemic disease activity was assessed using the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI, range 0–123) and ESSDAI without the biological domain (ClinESSDAI; range 0–135) (25, 26). Low disease activity was defined as ESSDAI <5, moderate disease activity as ESSDAI 5–13, and high disease activity as ESSDAI >13 (22). In addition, absolute number of B cells (10^9/L), IgG levels (g/L) and IgM-rheumatoid factor (RF; kIU/L) were measured in serum.

For all these clinical assessments, higher scores represent worse outcome.

Statistical analysis

Results were expressed as number of patients (%), mean ± standard deviation (SD) or median (interquartile range; IQR) for categorical, normally distributed and non-normally distributed data, respectively. Generalised estimating equations (GEE) with exchangeable correlation structure was used to analyse clinical assessments over time within patients. Since residuals were non-normally distributed, ESSDAI was log-transformed before entered into the equation.

Spearman correlation coefficient was used to investigate the relation of physical and mental fatigue on NRS with the MFI domains. To evaluate sensitivity to change, the standardised response mean (SRM) was calculated as the mean change score between baseline and 16 or 24 weeks divided by the SD of the change score. SRM <0.5 were interpreted as small, 0.5–0.8 as moderate, and >0.8 as large. *p*-values <0.05 were considered statistically significant. Statistical analysis was performed with IBM SPSS Statistics 22 (SPSS, Chicago, IL, USA).

Results

Of the 28 included patients with pSS, 96% were female, mean age was 43±14 years, median time since diagnosis was 5.3 years (IQR 3.8–9.9), and median ESSDAI was 8.0±4.5. Baseline characteristics are presented in Table I.

Importance of symptoms

At baseline, 24 (86%) patients reported physical fatigue as the complaint most eligible for improvement, followed by pain and dryness. Mental fatigue was ranked as the complaint least eligible for improvement by 12 (50%) patients (Fig. 1). However, for all these 4 domains, patients found it very important to get rid of their symptoms, reflected by median scores of importance for improvement of 8 or higher. As shown in Figure 1, the highest scores were again given for physical fatigue (median 10, IQR-10).

Also during follow-up, patients marked physical fatigue as most important for improvement.

Effect of rituximab treatment

Rituximab treatment resulted in significant improvement in patient-reported symptoms of physical fatigue, pain, dryness and mental fatigue, with maximum effects of all four domains seen at 16 or 24 weeks of follow-up (Fig. 2). A comparable course was found for absolute number of B cells, IgG levels, and IgM-RF (data not shown).

After rituximab treatment, the maximum absolute and relative improvement in median values at group level was 2.5 points and 31% for physical fatigue, 2.5 points and 36% for pain, 2.5 points and 36% for dryness, and 2 points and 36% for mental fatigue,

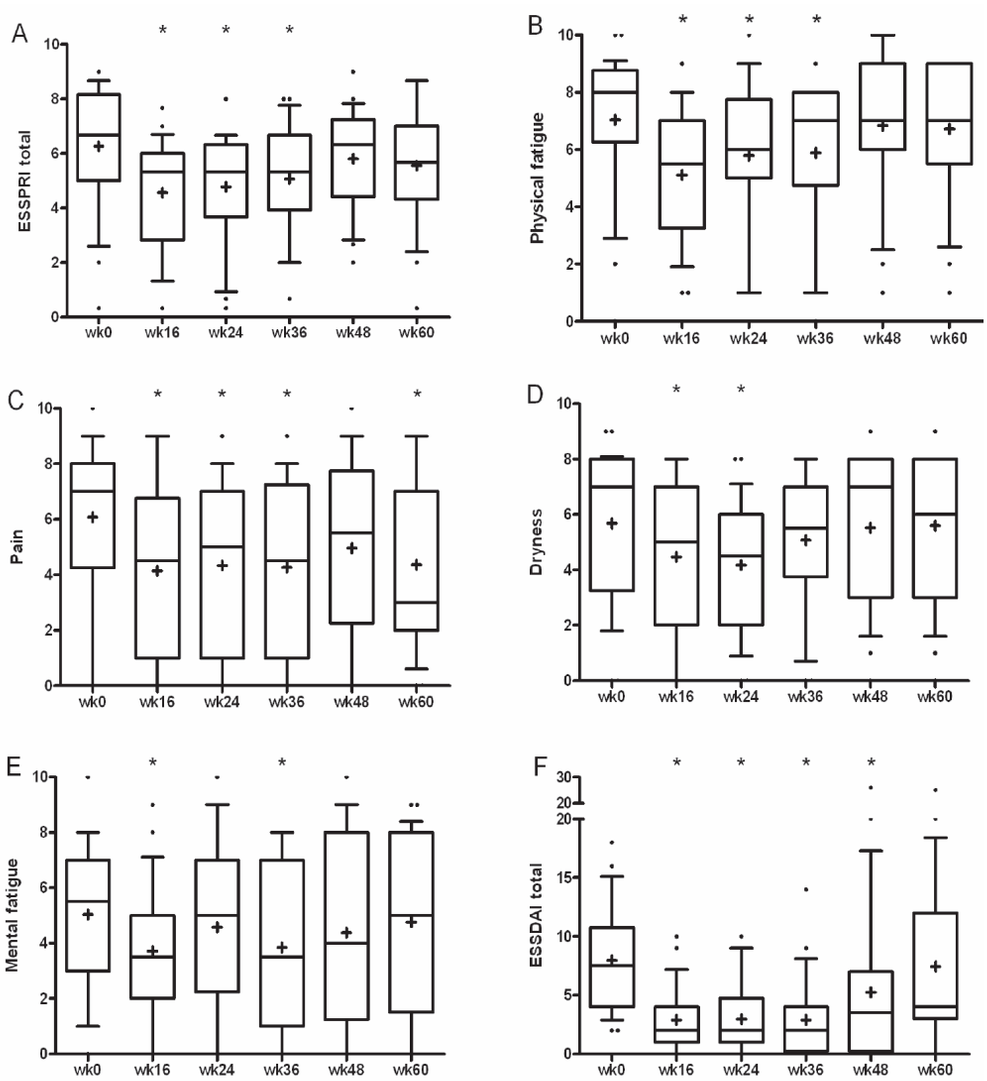


Fig. 2. ESSPRI total score (**A**), physical fatigue (**B**), pain (**C**), dryness (**D**), mental fatigue (**E**), and ESSDAI total score (**F**) during treatment with rituximab in 28 pSS patients.
Box-and-whisker plots: boxes indicate medians with interquartile ranges; + indicate means; whiskers indicate 10-90 percentile; • indicate outliers.
*Statistically significant compared with baseline.

respectively. The maximum improvement for the ESSPRI total score was 1.3 points and 20% at group level. In comparison, systemic disease activity assessed with ESSDAI improved 5.5 points and 73% at group level (Fig. 2).
Rituximab treatment also resulted in significant improvement in all domains of the MFI. General fatigue showed 25% improvement at group level, physical fatigue 19%, reduced activity 12%, mental fatigue 9%, and reduced motivation 16%. The maximum improvement for the MFI total score was 14% (Fig. 3).
At 60 weeks of follow-up, clinical assessments had returned to baseline values (Fig. 2-3).
GEE analysis over time revealed that physical fatigue was significantly associated with the absolute number of B cells (B=4.309, $p<0.001$) and the other patient-reported symptoms pain (B=0.429, $p<0.001$), dryness (B=0.249, $p=0.014$) and mental fatigue (B=0.487, $p<0.001$), but not with ESSDAI (B=0.057, $p=0.12$), ClinESSDAI (B=0.051, $p=0.12$), IgG levels (B=0.046, $p=0.17$) and IgM-RF (B=0.001, $p=0.43$).

Patient-acceptable symptom state
Before rituximab treatment, 18% of the patients had physical fatigue score <5, representing a satisfactory state according to the PASS. The proportion of patients with PASS for physical fatigue increased to a maximum of 36% after treatment. For the ESSPRI total score, patients with PASS increased from 25% at baseline to 43% after treatment. In comparison, the proportion of patients with low disease activity according to ESSDAI increased from 29% at baseline to 79% after treatment (Table II).

Physical fatigue as endpoint
Sensitivity to change of ESSPRI physical fatigue was large to moderate, with SRM of -0.95 at 16 weeks and -0.56 at 24 weeks. For MFI general and physical fatigue, SRM values were also large to moderate. In comparison, sensitivity to change of ESSDAI was large, with SRM of -1.19 at 16 weeks and -0.98 at 24 weeks (Table III).
ESSPRI physical fatigue showed the strongest correlation with MFI general fatigue ($\varrho=0.930$) and MFI physical fatigue ($\varrho=0.803$) at baseline. ESSPRI mental fatigue showed the strongest correlation with MFI mental fatigue ($\varrho=0.623$). Comparable results were

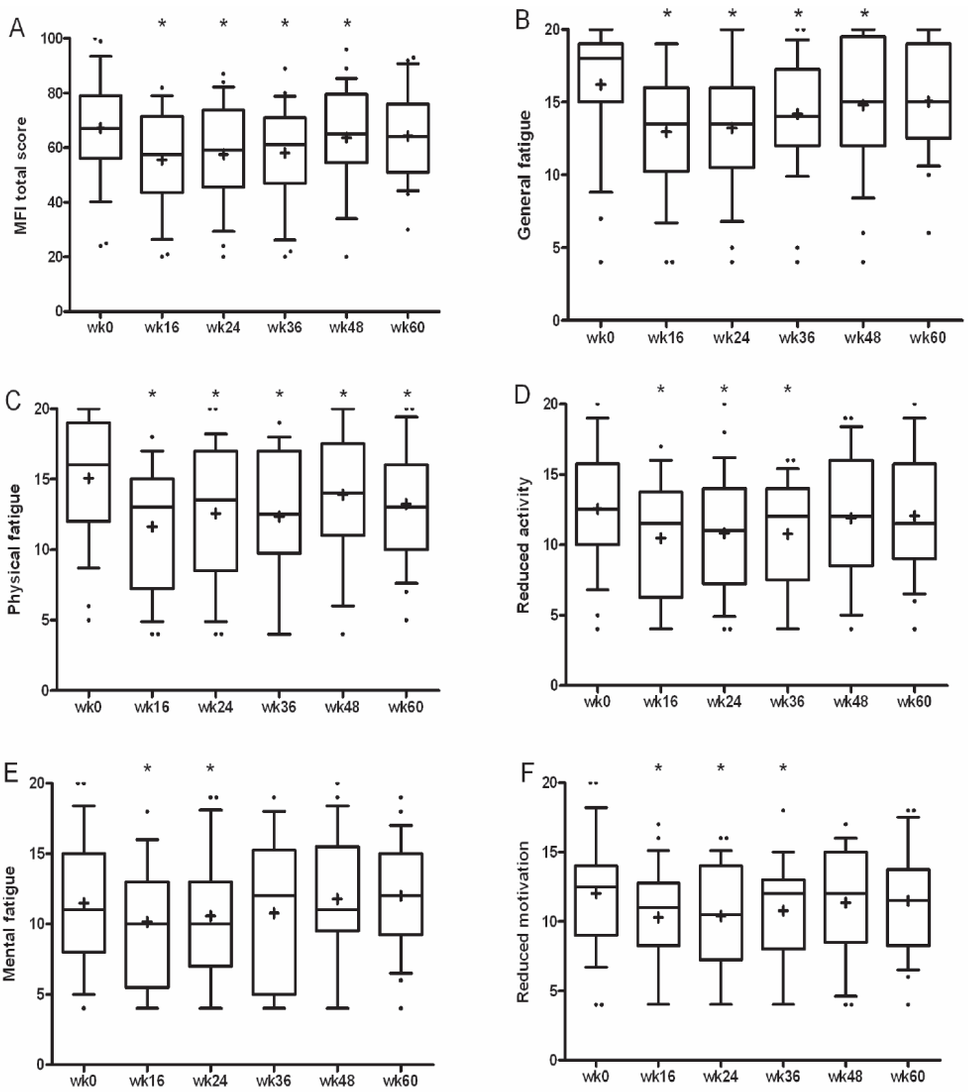


Fig. 3. MFI total score (**A**) and MFI domains (**B**-**F**) during treatment with rituximab in 28 pSS patients.
Box-and-whisker plots: boxes indicate medians with interquartile ranges; + indicate means; whiskers indicate 10-90 percentile; • indicate outliers.
*Statistically significant compared with baseline.

found at 16 and 24 weeks of follow-up (data not shown).

Discussion

In this post-hoc analysis of our open-label rituximab study in 28 pSS patients, we investigated patient experience regarding the importance of fatigue compared with other symptoms as well as the effect of rituximab treatment on fatigue.

Before the start of rituximab treatment, pSS patients rated the need to reduce their fatigue symptoms as very high, reflected by median scores of importance of 10 and 8 (out of 10) for physical and mental fatigue, respectively. Interestingly, the vast majority of patients (86%) reported physical fatigue as most eligible for improvement, more than symptoms of pain and dryness. Half of the patients ranked mental fatigue as least eligible for improvement. Previous studies also showed that physical fatigue is more severe and frequent than mental fatigue in pSS. In a cross-sectional study of 94 pSS patients, 96% reported somatic fatigue and 48% mental fatigue according to PROF scores >2 (1). In the development study of the ESSPRI in 230 pSS patients, dryness (39%), physical fatigue (32%), and limb pain (20%) were reported as most in need of improvement, whereas mental fatigue was least in need of improvement according to 47% of the patients (13).

In accordance, MFI scores were highest for general fatigue and physical fatigue in our study population. Multiple studies have shown that MFI scores are significantly worse in pSS patients compared with healthy controls (2, 27-30). After controlling for depression, differences in general fatigue, physical fatigue, and reduced activity remained statistically significant (27, 28). This confirms the presence of particularly physical fatigue in pSS.

The pathophysiological mechanism underlying fatigue in pSS is not yet elucidated, but is probably multi-factorial. Cytokines such as IL-6 and IFN-α, neuroendocrine disturbances, autonomic dysfunction, sleep disturbance, depression, anxiety, and tendomyogenic complaints have been suggested to be important factors in abnormal fatigue (5, 12). Previously, we demonstrated that B cell depletion with rituximab results in a significant reduction in serum levels of several cytokines/chemokines including IL-6 and IFN-α (31). In line with this notion, Barr *et al*.

Table II. Disease activity status before and after rituximab treatment in 28 pSS patients.

	Baseline	Week 16	Week 24
ESSPRI			
PASS total score (<5)	7 (25)	10 (36)	12 (43)
PASS physical fatigue (<5)	5 (18)	10 (36)	6 (21)
PASS pain (<5)	7 (25)	14 (50)	12 (43)
PASS dryness (<5)	9 (32)	12 (43)	14 (50)
PASS mental fatigue (<5)	13 (46)	17 (61)	13 (46)
ESSDAI			
Low activity (<5)	8 (29)	22 (79)	21 (75)
Moderate activity (5-13)	16 (57)	6 (21)	7 (25)
High activity (≥14)	4 (14)	0 (0)	0 (0)

Values are presented as number of patients (%).
ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; PASS: patient-acceptable symptom state; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index.

Table III. Standardised response mean (SRM) during rituximab treatment in 28 pSS patients.

	Week 16	Week 24
ESSPRI total score[22]	-0.86	-0.68
Physical fatigue	-0.95	-0.56
Pain	-0.53	-0.46
Dryness	-0.72	-0.61
Mental fatigue	-0.63	-0.20
MFI total score	-1.01	-0.84
General fatigue	-1.02	-0.81
Physical fatigue	-1.11	-0.74
Reduced activity	-0.91	-0.65
Mental fatigue	-0.38	-0.44
Reduced motivation	-0.59	-0.54
ESSDAI total score[22]	-1.19	-0.98

MFI: Multidimensional Fatigue Inventory; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index.

provided evidence that at least part of the beneficial effects of B cell depletion therapy on autoimmune disease can be explained by deletion of IL-6 producing B cells (32). Thus, our finding that in patients treated with rituximab, physical fatigue over time was significantly associated with the absolute number of B cells, may suggest that B cell derived IL-6 might be directly involved in this process. Unfortunately, these cytokines were not measured in this open-label study, so the direct relation with physical fatigue could not be analysed.

In this open-label study, rituximab treatment resulted in significant improvement in patient-reported symptoms of physical fatigue, pain, dryness, and mental fatigue. However, the improvement in subjective symptoms was much less than the improvement in objective systemic disease activity. Recently, the minimal clinically important improvement (MCII) of the ESSPRI was defined as a decrease of at least one point or 15% on NRS of 0–10 (22). A small study of 40 pSS patients assessed the minimally important difference (MID) of patient-reported outcomes on VAS of 0–100. Interestingly, the MID scores for improvement and worsening in fatigue were found to be different. A relatively small change in VAS fatigue (mean -6.2 mm) was perceived by the patient as an improvement, whereas a larger change (mean +15.2 mm) reflected worsening (33). At the group level, the median score of physical fatigue on NRS improved 2.5 points and 31% after rituximab in our study, which is more than the proposed MCII and MID scores. Overall, this improvement in physical fatigue seems thus to be clinically relevant.

Only a minority of our patients (36%) experienced physical fatigue below the cut-off value for the PASS after treatment. This means that although physical fatigue improved significantly after rituximab, most patients did not consider themselves in a satisfactory state. In comparison, 79% of patients reached low disease activity according to the ESSDAI, which represents an acceptable level of systemic disease activity. It should be kept in mind that the PASS was validated for the ESSPRI total score and may not be adequate for all individual symptoms (22).

A limitation of our open-label trial is that no control group was available. However, improvement in fatigue during rituximab treatment was also found in previous RCTs (16, 34). In a pilot study, 17 pSS patients with visual analogue scale (VAS) fatigue scores >50 were randomised to receive either 2 infusions of rituximab or placebo, in combination with steroids. At 6 months, there was a significant improvement in VAS fatigue in the rituximab group, but not in the placebo group. Comparable results were found for the somatic fatigue domain of the PROF (34). In the TEARS trial, 120 pSS patients with scores ≥50 mm on 2 or more of 4 VAS (global disease, dryness, fatigue, pain) were randomised to rituximab or placebo plus steroids. After adjustment for baseline characteristics, the mean decrease in VAS fatigue was larger with rituximab than placebo at 6, 16, and 24 weeks. Furthermore, fatigue responded better to rituximab treatment than the other patient-reported symptoms (16). However, both trials did not achieve their primary study endpoint, defined as >20% decrease in VAS fatigue in the pilot study and ≥30 mm decrease in 2 of 4 VAS at 24 weeks in the TEARS trial (16, 34).

Recent studies showed the potential value of biologic treatment such as rituximab, abatacept or belimumab. Thus far, there is no consensus about the primary endpoint of efficacy (35). A large cross-sectional study including 395 pSS patients demonstrated that patient-reported symptoms and systemic disease activity are complementary facets of pSS, reflected by very low correlation between ESSPRI and ESSDAI (19, 36). We found also very low correlations for ESSRPI total score as well as for the individual symptoms (data not shown). Furthermore, we showed that physical fatigue over time was significantly associated with other patient-reported symptoms, but not with ESSDAI. This again indicates that there is a discrepancy between patient experi-

ence of physical fatigue and objective systemic disease activity.

The sensitivity to change of the ESSPRI question on physical fatigue was large to moderate, but lower compared to the ESSDAI (23). ESSRPI physical fatigue correlated strongly with MFI domains general and physical fatigue. Based on these results, a single item question on physical fatigue seems worthwhile to include in clinical trials, preferably as secondary endpoint.

In conclusion, physical fatigue characterises patient experience of pSS. Patients rated physical fatigue as most eligible for improvement by treatment, more than symptoms of pain, dryness, and mental fatigue. Rituximab treatment resulted in a significant and clinically relevant improvement of physical fatigue. However, the large majority of patients did not achieve a satisfactory state and still experienced physical fatigue above the cut-off value for the PASS. Therefore, attention for optimal management of this prominent symptom is warranted in daily practice and future clinical trials in pSS.

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